

■ SPECIALTY UPDATE: KNEE

Allergy in total knee arthroplasty

A REVIEW OF THE FACTS

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We explored the literature surrounding whether allergy and hypersensitivity has a clinical basis for implant selection in total knee arthroplasty (TKA). In error, the terms hypersensitivity and allergy are often used synonymously. Although a relationship is present, we could not find any evidence of implant failure due to allergy. There is however increasing basic science that suggests a link between loosening and metal ion production. This is not an allergic response but is a potential problem. With a lack of evidence logically there can be no justification to use 'hypoallergenic' implants in patients who have pre-existing skin sensitivity to the metals used in TKA.

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Allergy in total knee arthroplasty (TKA) is an issue that has become increasingly prominent over the last few years. Implant companies are investing in and actively marketing hypoallergenic components, specifically for use in metal sensitive individuals despite an unclear immunological mechanism. With the number of patients undergoing primary TKA increasing annually and between 10% to 48%^{1,2} of the population being sensitive to metal, most commonly nickel, we aim to examine the literature and explore potential mechanisms of allergy. The literature was identified by searches on Medline and PubMed for articles with specific reference to allergy or hypersensitivity in total knee replacement whilst also aiming to improve our understanding of the basic science behind the processes of allergy and hypersensitivity.

Metallic implants are used widely in surgery including orthopaedics, cardiothoracics, vascular and maxillofacial surgery and dentistry. Whilst there are many individual case reports of localised and systemic effects related to metal implants^{3–5} there appears to be a lack of strong evidence to support or refute the hypothesis that this is caused by allergy. Similarly there are only a few case reports^{3,6} of painful standard TKAs with perceived allergy to the implants, that following revision to novel 'hypoallergenic' implants have been associated with resolution of the symptoms. This issue of perceived allergy to TKAs is likely to become more confused in the light of the problems surrounding metal on metal hip replacements where we know that failure is not

an allergic response.⁷ Legal action in Colorado, United States has been instigated against an implant company as a result of failed implants due to perceived allergy, with the manufacturer allegedly in breach of their duty to warn patients about the metallic components and their potential ability to cause an allergic reaction.⁸ There has been a degree of acceptance in some countries that metal related pathology may exist as demonstrated by the Australian Arthroplasty register where metal hypersensitivity was reported as the fifth most common cause for revision hip arthroplasty in the 2012 registry, making up 5.9% of all revisions.⁹ The wording was subsequently changed from 'metal sensitivity' to 'metal related pathology' in the 2014 report with 0.5% of all revision total hip arthroplasties (THA) associated with this term.⁹ The same change in terminology was used for TKA with metal sensitivity as a cause for revision in 1.3% of revisions in 2012 and in 2014, 1.8% of revision TKAs attributed to 'metal related pathology'.⁹ The terminology remains confusing and the polarised views demonstrates how divided opinion is on the existence and the implications of metal allergy as a deep implant-related phenomenon.

Allergy

Allergy is a complex spectrum of hypersensitivity disorder of the immune system. It is an over-reaction to a normally harmless substance. The classical definition of allergy in terms of hypersensitivity reaction is an immunologically mediated type I reaction. This reaction occurs as a

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consequence of antigen crosslinking with IgE causing mast cell degranulation and release of vasoactive biomolecules that has a response in seconds to minutes rather than days.¹⁰ This type of IgE mediated reaction does not occur in response to metal implants. Anaphylaxis after implantation of metal prostheses does not appear in the literature. Polymethylmethacrylate (PMMA) has been implicated as a cause of anaphylaxis in cases of death after using cemented fixation. This link is difficult to prove as cardiovascular collapse after cementing is well recognised as bone cement implantation syndrome.¹⁰⁻¹² Type IV hypersensitivity, on the other hand, is not antibody mediated but rather a T-cell lymphocyte mediated reaction taking a few days to occur in patients who have previously been sensitised to the allergen. This is the classical delayed type IV hypersensitivity reaction that encompasses contact dermatitis, with which, between 10% and 48%^{1,2,13,14} of the general population suffers. Metal particles on their own do not stimulate the immune system but must cross react with proteins. The resulting complex can then act as an antigen that can incite an immune response^{15,16} potentially in the form of T-cell mediated metal hypersensitivity. Metallic wear debris can occur in dynamic implants from the interaction of intended and unintended bearing surfaces as well as producing metal ions from the inevitable corrosion of metal from being in contact with liquid contained in tissues.¹⁷ Static implants can equally generate metal ions due to corrosion from being in contact with moist tissues without generating wear particles. Metal debris has been demonstrated to localise to the peri-implant tissues but to also to migrate to extra-articular tissue consistent with systemic dissemination of metal debris,¹⁸ including to bone marrow, lymph nodes and the liver.

Local and systemic response to metal

There has always been a question whether internal metallic devices can cause localised and systemic cutaneous manifestations similar to that seen in classical contact dermatitis. The Langerhans cells of the dermis are well characterised as the primary antigen presenting cells (APC) associated with dermal hypersensitivity. What is not clear is whether this cell line is responsible for the reaction of implant-related hypersensitivity. The following have been suggested as potential APCs: macrophages, endothelial cells, lymphocytes, Langerhans cells, dendritic cells and parenchymal tissue cells¹⁹ some of which may well be implicated in the dissemination of released metal ions and particles. The development of cutaneous reactions following the implantation of a TKA has been labelled as allergy and anecdotally some have shown resolution of symptoms following revision.²⁰ However there is no evidence of a causal link. Equally there is no link between development of cutaneous manifestations following TKA in patients who have been shown to be metal sensitive pre-operatively.²⁰ The development of cutaneous signs and symptoms following arthroplasty is rare^{15,21} and does not correlate with a pre-

operative diagnosis of contact dermatitis to the alloy components of metallic implants. There is an observed increase rate of patch test positive patients following implantation of metal including TKA²² and again there is no correlation between this increase in test positive metal hypersensitivity and cutaneous manifestation. In one paper prospectively looking at TKA and pre-operative testing for metal sensitivity, they showed 26% (24 of 92 patients) displayed a positive modified lymphocyte stimulation test (MLST) pre-operatively.²⁰ Of those five developed eczematous reactions (three localised to the knee and two generalised having started over the implant), all of which were positive MLST pre-operatively. Two were revised with resolution of the symptoms and their MLST changed from positive to negative. However, three further patients who had no additional surgery had gradual resolution of symptoms and also experienced a reversal of their previously positive MLST. The majority of patients in their study who had positive MLST for metal pre-operatively did not develop any skin reactions. In all, eight had a history of metal sensitivity and positive testing and 11 had no history of sensitivity, only two of the positive pre-operative tests were in men (22 females had positive MLST pre-operatively). Whilst the cellular and immunological mechanisms probably exist the pathway is not established and more importantly the clinical implications are unproven. The treatment for a cutaneous reaction should in the first instance be topical therapy with corticosteroid and this has had good results.²³

The local effects of metal ions

Perhaps a bigger issue than the development of cutaneous signs might be the unobservable local effects of metal hypersensitivity on the implant bone interface. Polyethylene debris has been studied in depth and the cellular pathway that leads to loosening has long been established.²⁴ In hips the biggest predictor of implant loosening is a linear wear rate of the polyethylene of greater than 0.1 mm per year.²⁵ Polymeric debris activates the innate or nonspecific immune system.²⁶ This type of immune response is the first line of defence immune system and does not initially include the pathways of allergy, this pathway as already discussed involves lymphocytes. Our accepted understanding of the immune system's response to a failing arthroplasty is that particulate matter causes an innate only or non-specific type of response. Functions of the innate immune system are as a first line host defence but also in antigen presentation to the specific or adaptive immune system. Hallab et al²⁷ demonstrated that there was an adaptive response by lymphocyte populations as a direct result of metal induced reactivity. Adaptive immune systems are cell mediated and use the attraction of other cell lines following stimulation or activation via the specific antigen.

The local effect of metal debris along with other particulate matter is not always predictable, however some generalisations have been made regarding the bio-reactivity of particles:

- The inflammatory response is proportional to the particulate load;²⁸
- Metal particles are more pro-inflammatory²⁹ than polymer-debris;
- Wear particle generation causes osteoclastic activation via macrophage ingestion.³⁰

Receptor Activator of Nuclear factor Kappa- B Ligand (RANKL) is the final common pathway for the activation of osteoclastic resorption of bone which in turn is stimulated by the release of pro-inflammatory activation factors such as interleukin (IL)-1beta, tumour necrosis factor (TNF)-alpha, IL-6 and prostaglandin E2 (PGE2)³¹ causing peri-implant osteolysis. This occurs with polyethylene debris related osteolysis and via a different pathway metallic debris can induce similar pro-inflammatory factors. Polyethylene, being the most abundant form of any plastic, would appear to not be implicated in causing contact dermatitis and so far no one has suggested that polymer allergy exists. These pro-inflammatory factors have also been shown not only to up-regulate osteoclastic activation but down regulate osteoblastic action.³² This degree of macrophage induced inflammation was analysed by Caicedo *et al*³³ who demonstrated that size and particle irregularity increased the inflammatory reaction initiated by macrophages ingesting metal alloy particles.

Implant loosening

Analysis of tissue following TKA has shown high levels of T-lymphocytes in peri-implant tissue around revised knees where the cause for revision was not infection, mal-alignment or malposition.³⁴ Both particulate and soluble material induce an inflammatory response, a recognised process that causes osteolysis and as a result, aseptic loosening of implants.¹⁵ It could be the case that some individuals are more at risk of developing loosening as a result of a heightened response to particulate and non-particulate debris but whether this heightened response is allergy is yet to be established.

The local tissue response to delayed type hypersensitivity reactions has been identified histologically being described as peri-vascular lymphocyte infiltration (PVLI) and diffuse lymphocytic infiltration (DLI), both have been demonstrated to be associated with the adaptive immune response that is seen in delayed type hypersensitivity.^{35,36} In a retrospective review of 242 revision TKAs, tissue samples were sent for histological analysis for PVLI and DLI, when 40% were found to have some degree of PVLI.³⁷ Similar peri-vascular tissue types were demonstrated in tissue from revision THA for metal on metal implant failure.^{35,36} This type of localised tissue response to metal on metal hip replacement has been associated with a delayed type hypersensitivity reaction that has been implicated in failing and failed metal on metal hips. Periprosthetic tissues have been studied in depth by The German consensus group.³⁸ Their revised classification includes a tissue type that they have postulated relates to an allergic reaction to the debris and contains a large proportion of lymphocytes.

Understanding that there might be a potential to label some forms of loosening as allergy is one thing but diagnosing metal sensitivity and knowing how to deal with the revision surgery, particularly with the implant choice is far more difficult. Significant conflicting opinion exists whether pre-operative screening for metal sensitivity is of any value, some accept that patients with existing allergy should undergo testing and the results should influence implant choice.²² However as stated there is no evidence to support this or to show a benefit to such an approach. When analysing failing implants diagnosis of the reason for failure is paramount to the success of a revision. Revising prostheses on the basis pain without a cause for failure is unlikely to resolve the situation nor is the patient likely to benefit.³⁹

Diagnosing allergy

Diagnosing allergy-related implant failure is we feel almost impossible and requires demonstration of:⁴⁰

- Typical T-lymphocyte rich immunohistopathology;
- Positive epicutaneous patch test to a specific implant-derived allergen;
- Healing of the response upon exchange of the implant to an immunologically inert implant.

Whilst the above could be considered as the minimum requirements for the demonstration of hypersensitivity the diagnosis is of questionable benefit as it can only be achieved by implant removal and resolution of the symptoms. In reality with so many confounding variables even resolution of the symptoms following revision is not adequate evidence for a scientific hypothesis.

A recent systematic review and meta-analysis of metal hypersensitivity testing in patients undergoing knee or hip arthroplasty reported that in patients who has a failed implant had twice the risk of having metal allergy compared with those who had a stable implant.²² Further analysis of the groups would not allow any prediction of the status of the implant when a positive hypersensitivity result was returned suggesting that the above finding may be an association rather than a causal relationship. Other studies have found that elevated levels of metal ions are seen in failed TKAs⁴¹ and suggested that chromium ion levels could be used when trying to diagnose the cause for failure of a TKA.

Whilst there is evidence to support the individual steps that hypersensitivity to metals might play a significant role in aseptic loosening in TKA there is no single study to support this hypothesis. In contrast there is registry data from Denmark that would strongly support the view that metal hypersensitivity is not relevant in THA.⁴² The authors concluded that there was no association between metal allergy and THA in patients linked by the Danish hip registry and the Danish patch testing registry. Whilst linking these two registries is potentially a very powerful tool in answering the question surrounding allergy in TKA its use is limited on two accounts. Firstly their population was that of THA not TKA and secondly only 0.5% of the THA population

of over 70 000 patients had a positive patch test, which is well below the expected number in the general population. This has to bring into question the validity of their detection rate of hypersensitivity and therefore the linked registries probably cannot help this debate.

Implant choice in hypersensitive patients

Making the choice to use standard implants in the light of patients with proven metal hypersensitivity has been backed up by a consensus of expert panel via a delphi study. They concluded that standard implants should be used irrespective of metal hypersensitivity, whether patient reported or a confirmed patch test.⁴³ Others will use hypoallergenic femoral components and an all polyethylene tibial component for patients who report metal hypersensitivity and who were positive in laboratory testing.⁴⁴ The most comprehensive systematic review of the topic in allergy concluded that hypersensitivity testing should be performed in patients with a history of metal hypersensitivity and suggested a treatment algorithm, that included testing for and not using if possible components to which the patient displayed hypersensitivity.²² This was not derived from the systematic review or meta-analysis but was purely an opinion expressed by the authors.

There is no question that metallic implants, both static and dynamic, generate wear debris that cause local reactions. This local reaction is not dose related nor predictable and therefore not purely due to the toxic effect of the debris but possibly due to an immunological host process. Hypersensitivity to metal undoubtedly exists but it cannot be stated at the moment to be an allergic reaction. Far greater than the problem of skin manifestations is the possibility that the reaction to metal debris might cause loosening. The mechanism for this to some degree has been established but has not been proven in a clinical setting. Research has focused on hip replacement in the light of the metal on metal arthroplasty problems and there is clearly a different magnitude to the load of metal debris⁴⁵ which is likely to represent a totally different scenario to allergy.

In conclusion, at the moment metal hypersensitivity as an allergic process cannot justify a revision in TKA but its importance and mechanism needs clarification. With the extensive and clinically unachievable criteria that needed to be fulfilled prior to diagnosis of allergy and need of evidence to support the use of hypo-allergenic implants we feel that there is no basis for the use of a peri-operative decision making algorithm to guide the clinician to use unproven hypoallergenic components. Patients with a diagnosis of metal hypersensitivity will however continue to ask about the materials used in their implants and they will always believe any problems they may have after their joint replacement are related to their pre-existing hypersensitivity. This topic requires greater scientific and clinical research to answer the question. Currently though there is no evidence that allergy exists in TKA and we will continue to use implants of standard material with proven longevity in all our patients.

Author contributions:

S. Middleton: Researched, wrote and prepared the manuscript.
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